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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,075	02/19/2004	Sean D. Monahan	Mirus.030.16.6	4417

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
12/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/782,075	MONAHAN ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,10,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,10,13,14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/25/2008 has been entered.

Status of Application/Amendment/Claims

Applicant's response 09/25/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 06/25/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 09/25/2008, claims 1, 4-6, 10 and 13-14 are pending in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites “wherein the hydrophobic group is selected from the list consisting of and membrane active compound." Claim 5 does not recite a list, only a membrane active compound. It is not clear if the hydrophobic group is further limited to a membrane active compound or if the composition comprises a hydrophobic group and a membrane active compound. For purposes of applying prior art, claim 5 is interpreted as composition comprising a hydrophobic group and a membrane active compound.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6, 10 and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, MPEP §2163 states, in part “…a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the

claimed invention." Moreover, the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by "…disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between functional and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

The instant claims are drawn to a composition comprising a modified RNA and a transfection reagent wherein said modified RNA consists of a functional group post-synthetically linked to an RNA via a labile bond cleavable under mammalian physiological conditions and wherein said functional group enhances interaction of said RNA with said transfection reagent, wherein the modified RNA is more resistant to nucleases and wherein a plurality of functional groups are attached to said RNA via labile bonds.

The instant claims and specification fail to provide adequate written description of the infinite number of hydrophobic groups that enhance the interaction of the claimed RNA with a transfection reagent.

The specification as filed discloses in Example 13 a post-synthetic amine-modified siRNA that increases nuclease protection and in Example 14 a post-synthetic hydroxyl modification of siRNA that also increases nuclease protection. The specification in Examples 1-12 further discloses acylated and silylated modified RNA and delivery of said siRNA into cells. The specification does not disclose a

representative number of species in the genus of all hydrophobic groups to provide adequate written description for the infinite number of siRNA modified with a hydrophobic group that provide the asserted function of enhancing the interaction of the siRNA with the transfection reagent. Moreover one of skill in the art would not know whether any hydrophobic group attached to a siRNA would have the necessary function of enhancing the interaction of the siRNA with any transfection reagent.

The specification as filed does not provide specific guidance that would lead one of skill in the art to the claimed invention. MPEP §2163 states, in part "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

Moreover, MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

Therefore, in the instant application, Applicants have not shown possession of the entire claimed genus of hydrophobic groups that when attached to the siRNA would enhance the interaction of the siRNA with a transfection reagent.

Applicants are reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-6, 10, 13 and 14 rejected under 35 U.S.C. 103(a) as being obvious over Fosnaugh et al. (US 2003/0143732), Manoharan, M. (Biochimica et Biophysica Acta 1489, 1999: 117-130) and Goldsborough (of record PTO Form 892 11/29/2005).

The instant claims are drawn to a composition comprising a modified RNA and a transfection reagent wherein said modified RNA consists of a functional group post-synthetically linked to an RNA via a labile bond cleavable under mammalian physiological conditions and wherein said functional group enhances interaction of said RNA with said transfection reagent, wherein the modified RNA is more resistant to nucleases and wherein a plurality of functional groups are attached to said RNA via labile bonds.

For purposes of applying prior art, the limitation “wherein said hydrophobic group enhances the interaction of said RNA with said transfection reagent” is interpreted very broadly. The specification does not define what “enhances the interaction" of a siRNA with a transfection reagent. Applicant points to page 3, lines 26-32 which states"

> “In a preferred embodiment, we describe methods to alter the interaction of an siRNA with a cell or transfection agent comprising: reacting the siRNA with a modifying agent wherein the modifying agent contains a hydrophobic group. The transfection agent can comprise polymers, lipids, detergents, or surfactants, or a combination of polymers, lipids, detergents, or surfactants. Hydrophobic modification of the siRNA allows hydrophobic interaction of the siRNA with the transfection agent.”

The instant specification does not describe which hydrophobic groups enhance the interaction of the siRNA with a transfection agent and does not describe what encompasses the tem "enhances". The term enhances is interpreted to mean any interaction of a siRNA molecule comprising a hydrophobic group with a transfection agent such that the siRNA is capable of entering a cell. Therefore, a siRNA which consists of any hydrophobic would allow interaction of the siRNA with the transfection agent and therefore would alter i.e. enhance the interaction of a siRNA with a transfection agent.

Lewis et al. teach compositions comprising RNA compounds such as siRNA or antisense wherein the antisense compounds comprise 2’- modifications (see paragraph 0042). Lewis et al. teach the RNA compounds are attached to functional groups used to aid in the delivery of the RNA compound to the cell as well as enhance the stability of the complex and teach when attached to functional groups, the functional group alters the interactions of the complex to the attached group and teach such functional groups

are cell targeting compounds and hydrophobic groups such as lipids and also carbohydrates (see paragraph 0112). Lewis et al. further teach multiple functional groups can be attached (see paragraph 0032). Lewis et al. teach the functional groups are attached via labile bonds that can be selectively broken and dissociated to provide an active inhibitor in the cell (see paragraphs 0120-0128). Lewis et al. do not specifically teach attachment of the functional groups such as lipids at the 2' position of the ribose nor teach the modified siRNA comprising silylated, acylated or alkylated RNA.

Goldsborough disclose the RNA can consist of a silylated RNA (see page 25), an acylated RNA (see page 20) or an alkylated RNA (see page 21). Goldsborough disclose the modified RNA consists of a functional group attached to a ribose 2'-hydroxyl position (see page 41), the modified RNA has more than one, but not all of the ribose 2-hydroxl positions modified (see page 13) and the modified RNA are more resistant to nucleases (see Example 61). Goldsborough disclose a modified RNA molecule comprising a functional group at the 2'-hydroxyl position (see page 21) and wherein the functional groups increases the RNA molecules stability which would enhance delivery of the RNA to a mammalian cell.

Manoharan et al. teach efficient conjugation of conjugates such as carbohydrates and other ligands at the 2' position of the RNA (see page 124).

It would have been obvious to conjugate functional groups to RNA at the 2' hydroxyl position of the RNA, as taught by Manoharan. It would have further been

obvious to incorporate modified silylated RNA, acylated RNA or alkylated RNA into RNA molecules, as taught by Goldsborough.

One of skill in the art would have been motivated to incorporate modified silylated RNA, acylated RNA or alkylated RNA into RNA molecules because Goldsborough teach incorporating silylated RNA, acylated RNA or an alkylated RNA into a RNA molecule protects the RNA from degradation. Goldsborough teach RNA is inherently unstable and protecting RNA from degradation while maintaining the biological activity of RNA is essential for use by one of skill in the art (see pages 3-4). Goldsborough et al. teach modified RNA molecules would have enhanced activity compared to natural RNA molecules because they are more stable and able to enter the cell more readily (see page 71). Further, one of skill in the art would have been motivated to attach the functional group to the 2' hydroxyl position of a RNA given Manoharan teach this position improves the chemical properties such as stability and nuclease resistance of said RNA molecules.

Finally, one would have a reasonable expectation of success because Goldsborough teach successful incorporation of a silylated RNA, acylated RNA or an alkylated RNA into a RNA molecule and further teach incorporation of such RNA does not affect the biological activity of the modified RNA. Moreover, one would have expected to conjugate a functional group to the 2' hydroxyl position of a RNA give Manoharan et al. teach efficient RNA molecules with enhanced properties when functional groups are attached at the 2' position.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 1, 4-10, 13 and 14 under 35 U.S.C. 103(a) as being obvious over Fosnaugh et al. (US 2003/0143732), Manoharan, M. (Biochimica et Biophysica Acta 1489, 1999: 117-130) and Goldsborough (of record PTO Form 892 11/29/2005) is maintained for the reasons of record in the Office action mailed 06/25/2008.

Applicant's arguments filed 09/25/2008 have been fully considered but they are not persuasive. Applicant submits that the claims amendments obviate the rejection and point to support for the claim amendments. Applicant has not provided any argument as to why the claim amendments distinguish over the rejection of record. Fosnaugh et al. teach conjugates comprising siRNA and functional groups such as hydrophobic lipids that are attached to the siRNA via biodegradable linkers. It appears Applicant has amended the claims to overcome the rejection of record based on the Examiners statement in the previous Office action that the claims do not require the modification to be responsible for enhancing the interaction of the RNA. However, it was further explained that based on the description of they hydrophobic modification on page 3 any functional group that is hydrophobic would enhance the interaction of the RNA with the transfection reagent. Fosnaugh et al. teach the functional groups can be lipids, which are hydrophobic and teach the conjugate can be mixed with transfection reagents for delivery to cells. Therefore, the attachment of the lipid functional group would enhance the interaction of the RNA with the transfection reagent and Applicant

has not argued why the hydrophobic group taught by Fosnaugh et al. would not enhance the interaction of the siRNA with the transfection reagent.

Thus, instant claims are obvious over Fosnaugh et al., Manoharan, M. and Goldsborough and the rejection is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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/Kimberly Chong/
Examiner
Art Unit 1635